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| EXAMINER | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/510,971 | KOJIMA, TETSUO | |
| | Examiner | Art Unit | |
| | LYNN BRISTOL | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *21,33 and 43-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,33 and 43-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/29/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 21, 33, 43, and 45-53 are all the pending claims for this application.

2. Claims 19, 20, 22, 31, 32, 34 and 44 were cancelled, Claims 21, 33, and 43 were amended, and new Claims 45-53 were added in the Response of 9/29/09.

3. Claims 21, 33, 43, and 45-53 are all the pending claims for this application.

4. Applicants amendments to the claims have necessitated new grounds for objection and rejection. This Office Action is final.

### *Information Disclosure Statement*

5. The information disclosure statement filed 9/29/09 has been considered and entered. The examiner's initialed copy of the 1449 form from the IDS is attached.

### ***Rejections Maintained***

### *Claim Rejections - 35 USC § 112, first paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### *Written Description*

6. The rejection of Claims 21, 33, 43, and 45-53 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained

For purposes of review, the rejection was set forth in the Office Action of 4/15/08 as follows:

"Claims 19-30 are interpreted as being drawn to methods for constructing a single chain diabody library, Claims 31-42 are interpreted as being drawn to methods for producing a construct encoding a single chain diabody library, and Claims 43 and 44 are interpreted as being drawn to a method for constructing an antibody library, where the methods require a "a linker of 30 to 150 base pairs comprising a cleavage site for a restriction enzyme", or b) a "linker of 30 to 150 base pairs comprising a cleavage site for a first restriction enzyme and a cleavage site for a second restriction enzyme that is different from, the first restriction enzyme", or c) "a linker of 30 to 150 base pairs comprising two or more cleavage sites for a restriction enzyme."

The linker molecules in addition to being required to possess these structural characteristics must also upon translation into a peptide linker allow for the proper folding of the sc diabody or scFv for antigen binding. As taught by Volker et al. (Volkel (Protein Engineering 14(10):815-823 (2001); cited in the IDS of 5/25/06):

"A scDb had a preferred length of 15 or more amino acid residues for the middle linker M and of 3-6 residues for the linkers A and B. No obvious bias towards a preferred linker sequence was observed. Reduction of the middle linker below 13 residues led to the formation of dimeric scDb, which most likely results from interchain pairing between all the V(H) and V(L) domains. Dimeric scDb were also formed by fragments possessing a long linker M and linkers A and B of 0 or 1 residue. We assume that these dimeric scDb are formed by intrachain pairing of the central variable domains and interchain pairing of the flanking variable domains."

Therefore, the claims encompass a genus of molecules defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property.

The specification teaches "a "linker" is not specifically limited as long as it does not interfere with expression of the antibody variable domains that are connected at both of its ends; the linker may or may not comprise restriction enzyme sites. Herein, a "long linker" means a linker of a size that enables the antibody heavy chain and light chain variable domains to be present as a scFv when the domains combined with the linker are expressed in a phage library. The length is not particularly limited, but preferably 30 bp to 150 bp, more preferably 36 bp to 90 bp, and most preferably 45 bp to 60 bp. Similarly, a "short linker" means a linker of a size that enables formation of a diabody (Db) when antibody heavy chain and light chain variable domains are combined with the linker and expressed. The length is not particularly limited, but preferably 6 bp to 27 bp, more preferably 9 bp to 21 bp, and most preferably 12 bp to 18 bp" [0058]; restriction sites are listed on p. 11, lines 8-12; and "For example, in the above case where BamHI and AccIII are used in a phage antibody library directed against antigens A and B, a fragment may be cut out using another restriction enzyme, such as SfiI, and inserted into an appropriate vector, as shown in FIG. 1" [0059]; and "For example, when phage libraries are constructed, two BamHI sites (underlined) can be designed within the linker, as below: TABLE-US-00002 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySerGlyGlyGlySer (SEQ ID NO: 3) GGTGGTGGTGGATCCGGTGGTGGTGGTTCTGGCGGCGGCGGCTCCGGAGGTGGTGGATCC (SEQ ID NO: 4)" [0080].

Accordingly, there is insufficient written description encompassing any one of the three linkers above because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics are not set forth in the specification as-filed, commensurate in scope with the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

In the absence of structural characteristics that are shared by members of the genus of a "linker" of a), b) or c); one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

## The rejection was maintained in the Office Action of 4/1/09 as follows:

"Applicants allegations on pp. 9-15 of the Response of 1/13/09 have been considered and are not found persuasive. For purposes of brevity, their comments are excerpted as follows: Applicants allege based on the flow diagrams depicting the method of Claims 19 and 21 as presented in Exhibits A and B, respectively; the specification disclosure at paragraphs [0005, 0006, 0007, 0053, 0054, 0058, Figures 1 and 2); and the Volkel reference (Volkel, Protein Engineering 14( 10): 815-823 (2001)), that the claims are fully supported for the method of making the diabody library using the instant claimed nucleotide linkers.

Response to Arguments

Each of the schematics in Exhibits A and B depicts what is an alleged optimum embodiment for performing the method in order to produce a diabody. The examiner reiterates what was discussed during the interview of August 28, 2008, namely, that the linker length between, for example, "L1 and L2" and "H2 and H1" for element (e) of Exhibit A (method of Claim 19), and the linker length between "L1 and L2" and "H2 and H1" for element (e) of Exhibit B (method of Claim 21) is undefined in the instant claimed method. Applicants have not demonstrated a structure/function correlation for the genus of claimed linkers that would allow the proper translation and folding of each scFv in the diabody in order to bind the respective target antigens.

It was further discussed during the interview, that the nucleotide linkers (30 to 150 base pairs) for any of the generic methods is required to a) have any restriction enzyme site positioned anywhere in the linker for the L1-L-H1 scfv; and b) translate into a linker of from *10 to 50 amino acids*. Thus, many possible scenerios for the first linker of the L1-H1 scfv of any given diabody are encompassed by the claims. So for example, when the L2-L2-H2 scFv is inserted into the L1-L1-H1 scFv, the linker on one side of the L2-L2-H2 scFv can be a single amino acid while on the other side it can be nine amino acids, e.g., (L1-(1aa L)-(L2-(L)-H2)-(9 aaL)-H1) *or* (L1-(9aa L)-(L2-(L)-H2)-(1 aaL)-H1); and myriad other possibilities are encompassed , e.g., (L1-(2aa L)-(L2-(L)-H2)-(8 aaL)-H1) *or* (L1-(8 aa L)-(L2-(L)-H2)-(2 aaL)-H1); (L1-(1 aa L)-(L2-(L)-H2)-(49 aaL)-H1) *or* (L1-(49aa L)-(L2-(L)-H2)-(1 aaL)-H1); (L1-(2aa L)-(L2-(L)-H2)-(48 aaL)-H1) *or* (L1-(48 aa L)-(L2-(L)-H2)-(2 aaL)-H1); etc. Applicants specification does not nearly define much less support the total possible scenerios for the linkers of the instant claims because Applicants did not contemplate the structure and function required for the myriad linkers. Applicants did not contemplate the proper pair-wise association for the L1 and H1 domains in any given construct because the claims encompass linkers that would not achieve this pairwise formation.

Further and under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised training materials from 3/29/08), the claimed invention must meet the following criteria as set forth.

a) Actual reduction to practice: The specification discloses the linker is selected "so long as it does not interfere with the expression of the antibody variable domains that are connected at both of its ends" (p. 12, lines 7-10). The specification teaches cloning and isolation of a diabody library using the polynucleotide linkers comprising :

SEQ ID NO:1- (p. 11);
SEQ ID NO:2- (p. 11); and
SEQ ID NO:4- (p. 18).

Finally, the specification teaches "Next, the phage library, or genes comprising the variable domains prepared from the phage library (for example, phagemids ) concentrated from each library by panning and such, or genes amplified by PCR from the above phage library), are treated with BamHI, and self-ligated *to reduce the length of the linker from 20 amino acids for scFvs to five amino acids, which is most suitable for diabodies* ("GlyGlyGlyGlySer (SEQ ID NO: 6)" encoded by "GGTGGTGGTGGATCC (SEQ ID NO: 5)")." Thus the specification does not demonstrate making a diabody library with just any polynucleotide linker of any composition and the length of 30 to 150 base pairs and having just any restriction site located anywhere in the linker.

b) Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the genus of polynucleotide linkers. The Exhibits A and B do not further define the structures of the linkers.

c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the genus of polynucleotide linkers.

d) Method of making the claimed invention: the specification teaches the method steps for making the diabody libraries using the linkers of SEQ ID NO: 1, 2 , 4 or 5.

e) Level of skill and knowledge in the art: the cloning of scfvs and generating diabodies was well established at the time of the invention.

f) Predictability in the Art: the art does not appear to teach the myriad polynucleotide linkers encompassed by the claims much less comprising just any restriction site much less where in the linker the restriction site can be located, and which can be properly expressed to allow for proper folding of the scfvs into a diabody with antigen binding properties. Hudson et al. (J. Immunol. Methods 231:177-189 (1999); cited in the IDS of 5/25/06) teaches that "A precise definition of the N- and C-terminal residues of the V-domains is required when designing the linker length" (p. 180, Col. 1, ¶ 1). A linker of 5 residues favors the folding of scfv as a diabody (Rousch et al., Br. J. Pharmacol., 125: 5-16 (1998)).

Applicants have not demonstrated with sufficient evidence the genus of polynucleotide linkers of 30 to 150 base pairs having any restriction site located anywhere within the linker and which translate to permit the expression and folding of the scfvs into a diabody format with retention of binding for the respective antigens. The ordinary artisan could reasonably conclude that Applicants were not in possession of the claimed genus of polypeptide linkers at the time of application filing.

In response to applicant's argument that the specification and Volkel reference show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., nucleotide linkers of SEQ ID NOS:

1, 3 and 5) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).
The rejection is maintained."

Applicants allegations on pp. 7-9 of the Response of 9/29/09 have been considered and are not found persuasive. Applicants allege that in amending Claims 21 and 33 are amended to specify that the first and second nucleotide linkers are 45 to 60 base pairs in length, and further to specify that the two restriction sites in the first nucleotide linker are located such that treatment with the two restriction enzymes and subsequent ligation result in a pair of linkers, each encoded by 6 to 27 base pairs and corresponding to 2 to 9 amino acids has overcome the rejection. Applicants allege because the length of the linker is the only important variable in defining how it functions, the presently claimed methods would be expected to produce single chain diabodies that function appropriately.

Response to Arguments

The Examiner submits that Applicants' counsel is not yet able to grasp or comprehend the technical scope of the first and second nucleotide linkers encoding the peptide linkers and comprising any nucleic acid residues much less where each comprises one or more restriction enzyme (RE) site(s) from amongst the myriad RE's recognized in the art. A simple search of a commercial RE supplier, e.g. New England Biolabs, shows that several different enzymes recognize distinct and unique restriction sites in nucleotides (see attached list of enzymes). Thus Applicants have placed an onerous and unreasonable burden on the Office to play the role of instructor insofar as explaining which nucleotide sequences comprising the critical RE sites and encoding

the peptide linker fall within the bounds of written description support. The detailed explanation of an invention is seemingly one that would occur between the Applicant and their counsel.

In order to place applicants in possession of the scope of claimed linkers that allow proper excision, expression, assembly of the single chain diabody, and diabodies having an antigen binding capability, Applicants must have demonstrated at the time of filing a structure/function correlation for a reasonable number of those linkers. The Examiner has delineated and applied the written description analysis based on the guidelines in the previous Office Action and Applicants have not even responded with technical or legal arguments why the Examiner's conclusions are improper. Applicants specification and the art have not identified sufficient relevant identifying characteristics for 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the genus of first and second polynucleotide linkers having all of the required structural and functional properties of the claims.

The rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. The rejection of Claims 21 and 33 under 35 U.S.C. 103(a) as being unpatentable over Little et al. (CA 2331641 or DE19819846; published 11/11/99; both cited in the IDS of 5/25/06) in view of McGuinness et al. (Nat. Biotech. 14:1149-1154 (1996); cited in the PTO 892 form of 8/8/07) and Volkel (Protein Engineering 14(10):815-823 (2001); cited in the IDS of 5/25/06) is maintained.

The rejection was maintained in the Office Action of 4/1/09 as follows:

"The interpretation of the claims is of record.

The claims were prima facie obvious at the time of the invention in view of Little, McGuinness and Volkel.

See Figure 2 of Little (DE19819846), where Little shows restriction digestion of a first linker in a first scfv; restriction digestion of a second linker in a second scfv and recombining the VH1-VL2 and the VH2-VL1 constructs into a single fused scfv diabody construct for producing libraries.

McGuinness discloses methods for constructing an antibody phage display library where the V regions from antibodies against the hapten phOX or Dig are constructed into two pools of scFvs repertoires having a 15-amino acid linker between each VH and VL domain, where the orientation of the domains is VH-linker-VL (p. 1150, Col. 1, ¶1). The scFv pools were recombined into a diabody format: VHA-VLB-rbs (linker)-VHB-VLA, where the linker between each VH and VL domain was "shortened" to a zero linker (p. 1150, Col. 2, ¶1) using one of two methods: ligation mediated assembly or cassette cloning where the final diabody is inserted into an expression vector. For ligation-mediated assembly, a two- (Fig 21, A-C) or three-step (Fig. 2iD) process is taught in the Materials and Methods on p. 1153, ¶2. In the three-step approach, an 800 bp fragment comprising Dig VH-phOxVL and phOxVH fragment are cut with a restriction enzyme and ligated, then the ligated fragment was mixed with a Dig VL fragment and digested with another restriction enzyme, and then ligated to produce the diabody insert. The two-step approach comprised taking the 800 bp fragment comprising Dig VH-phOxVL and phOxVH and a phOxVH-DigVL fragment, ligating the mixture and digesting with restriction enzymes to produced the diabody insert. For cassette cloning, VHA-VLB and VHB-VLA fragments were generated by PCR extension from the scFv pools, and the fragments digested with different restriction enzymes (Fig. 2ii) to produce a DigVH-phOxVL fragment and a phOxVH-DigVL fragment with terminal restriction sites followed by assembly into the diabody (p. 1151, Col. 1, ¶2; and M & M, p. 1153, Col. 2, ¶2). The 15 amino acid linker of McGuinness is considered as reading on the linker for the first and second single scFvs and the HV and LV. The claims are not drawn to the specific order in which the VH1 and VL1 or the VH2 and VL2 should occur. In other words, McGuinness teaches a diabody format: VHA-VLB-rbs (linker)-VHB-VLA which reads on the instant claims. Thus McGuinness teaches at least two possible methods for producing a scfv diabody format or

construct, but more importantly, that the ordinary artisan could predict that scfv diabody libraries were producible at the time of the invention much less functional based on McGuinness.

Volkel discloses constructing a diabody phage display library comprising single chain diabody CEA scFv/Gal scFv constructs with a randomized middle linker from where the M linker is of variable length and comprises at least one restriction site (See Figure 2A and B). Volkel discloses generating a fragment comprising GalVL-M linker-GALVH where the M linker comprises a restriction site and subcloning the fragment into the linker region for the CEA scFv where the linker region comprises two restriction enzyme sites, BstE II and Sac I. Volkel discloses generating clones with variable linker and M-linker lengths and comprising different amino acid sequences (Tables III and IV) which are cloned into an expression vector.

One skilled in the art would have been motivated and been assured of reasonable success in having produced the instant methods at the time of the invention based on the combined disclosures of Little McGuinness and Volkel because each disclose the technology for constructing single-chain diabody phage display libraries where a scFv recognizing a first antigen comprising a linker with a restriction enzyme site and a second scFv recognizing a second antigen comprising a linker are treated with a restriction enzyme in order to obtain fragments which are then ligated in order to construct a final fragment having the VH and VL domains against the second antigen inserted between the VH and VL domains against the first antigen are assembled into the diabody phage display library. Each of the references discloses techniques involving differential restriction enzyme digestion of various fragments and the technology for selective insertion of the VH2/VL2 or VL2/VH2 pair between the VH1/VL1 or VL1/VH1 domains to generate a phage display diabody library. Each of the references teaches obtaining fragments comprising variable domains and shortening the linker between the domains in a ligation (PCR extension step). Further because the instant claimed method actually involves even fewer steps than taught by any of the reference disclosures in order to generate a scfv diabody construct, the ordinary artisan would have been motivated to obtain a process that was ensured to generate functional scfv diabody, by inserting a sequence encoding a second pair of heavy and light chain variable domains into the open restriction site for the linker of a first pair of heavy and light chain variable domains.

Based on the combined reference disclosures, one skilled in the art could have been assured of success in introducing linkers between VH and VL domains comprising restriction sites for subcloning into or between VH and VL domains against a different antigen because the references taught that subfragments could readily be generated and where a VH/VL pair against one antigen was inserted between the VH and VL against a different antigen. Little and McGuinness teach that construction and selection from such a library is possible and it avoids unfavorable combinations (p. 1153, Col. 1, ¶2), and Volkel discloses generating single-chain diabodies with optimized linker sequences and expressed by phage display where correctly folded molecules can be screened against a variety of different target cells and antigens (p. 822, Col. 2, ¶3). Further, one skilled in the art could have readily constructed a self-ligating antibody library based on the method steps of Little, McGuinness and Volkel to produce a second library having a shorter linker in relying on restriction enzyme sites in linker to restrict out a certain length of the linker to obtain a shorter linker.

Under the recent KSR decision, the cited references of art are not required to "*explicitly* teach or suggest" all of the method steps. The Supreme Court has determined in *KSR International Co. v. Teleflex, Inc.*, 550 U.S._, 82, USPQ2d 1385 (2007), that "a person of ordinary skill attempting to solve a problem will" not " be led only to those elements of prior art designed to solve the same problem……." (KSR, 550 U.S. at_, 82 USPQ2d at 1397). In addition, the court found that "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variant, 35 USC 103 likely bars its patentability" (KSR, 550 U.S. at_, 82 USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way, in particular by concluding "that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'" (KSR, 550 U.S. at_, 82 USPQ2d at 1397) and has further determined that "…….[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" (KSR, 550 U.S. at_, 82 USPQ2d at 1395). The court further found that "…… the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious" (KSR, 550 U.S. at_, 82 USPQ2d at 1395-1396). *Thus, when considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established known use.*"). Thus in general, the combined art reference disclosures teach that the skilled artisan could reasonably predict inserting a sequence encoding a second pair of heavy and light chain variable domains into the open restriction site for the linker of a first pair of heavy and light chain variable domains, would produce a library of functional diabodies. It is the examiner's position that Applicants have not provided an improvement over the combination of known elements already disclosed in the prior art at the time of the invention."

Applicants allegations on pp. 9-15 of the Response of 9/29/09 have been considered and are not found persuasive. Applicants allege "The experiments illustrated in Figure 2 are described in Example 1 of Little et al., beginning at page 10 of this reference. Little et al. started with two scFv constructs and employed PCR to introduce the desired linkers in the final constructs"; "In marked contrast to Little et al.'s scheme, the presently claimed method does not need to utilize PCR to introduce any of the three linker sequences, all of which are present in the starting constructs"; "Further, unlike the Little et al. scheme, which initially separates the two pairs of variable domains into four different constructs and then reassembles them into two and finally one construct, Applicant's methods split only one of the two pairs, leaving the other pair of variable domains attached to each other'; "MGuinness does not disclose ligating a sequence encoding a second pair of heavy and light chain variable domains to those cleaved restriction sites, thereby producing a construct encoding a single polypeptide containing two heavy and two light variable domains, all linked by linkers of the lengths defined in claim 21"; and "Volkel was not concerned with combining two libraries, each encoding two-variable-domain single chain antibodies, to prepare a four-variable-domain, single chain diabody library, and in fact started out with a construct that already contained all four variable domains in a single chain,..."

Response to Arguments

An element that is important or essential cannot be removed from a prior art reference in setting forth an obviousness rejection, see Eisai Co. v. Dr. Reddy's Laboratories, 533 F.3d 1353, 1358 (Fed. Cir. 2008) (noting in regard to obviousness,

that the record provided no reason to start with a lead compound and then drop the feature of the lead compound that leads to its advantageous properties). However, the ordinary artisan would not have considered the PCR step of an essential step, such that its removal would render the method of Little inoperable.

Applicants argument is not found to be convincing that since Little did not teach libraries it would not have been obvious to apply MGuinness or Volkel to achieve a larger scale of the same resultant product as claimed. First, it is not a requirement that the Examiner establish that the cited art contains all the elements of the rejected claim, as the analysis under 35 U.S.C. § 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR, 550 U.S. at 418. As found by the Examiner, to insert a first VH-peptide-VL construct into a pre-existing or second VH-peptide-VL construct based on digesting the constructs with restriction enzymes within the nucleic acid portion encoding the peptide, would have been well within the skill of the ordinary artisan at the time of the invention in view of the available high level technology for recombinant antibody technology as evidenced by the cited reference art of record.

The rejection is maintained.

***New Grounds for Objection***

***Claim Objections***

8. Claims 45-53 are objected to because of the following informalities: The claims recite sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, the claims fail to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) that they do not recite the sequence identifier for the peptide sequences.

Appropriate correction is required.

***New Grounds for Rejection***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 45, 48 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 45, 48 and 51 are indefinite for the recitation "wherein the amino acid sequence of the peptide linker contains one or more copies of the sequence GlyGlyGlyGlySer" and in depending from Claims 21, 33 and 43. A single "GlyGlyGlyGlySer" peptide is encoded by 15 base pairs, however the corresponding generic claims require that the first and second nucleotide linkers encoding the peptide linkers are of 45 to 60 base pairs, and therefore, the number of base pairs encoding a

single peptide of Claims 45, 48 and 51 does not fall within this range but below this range.

By similar reasoning, Claims 45, 48 and 51 also recite that the peptide linker may comprise "one or *more* copies of the sequence of GlyGlyGlyGlySer" where the upper limit of copies is infinite. So in the instance where the number of peptide linker copies exceeds 4, then the number of base pairs encoding those peptides does not fall within the range of 45 to 60 base pairs but above this range.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***Written Description/ New Matter***

10. Claims 45, 48 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 45, 48 and 51 are interpreted as being drawn to "one or *more* copies of the sequence of GlyGlyGlyGlySer."

The examiner's search of the specification for the limitation does not identify literal support for this limitation. (MPEP 706.03(m) states in part "New matter includes not only the addition of wholly unsupported subject matter, but may also include adding

specific percentages or compounds after a broader original disclosure, or even the omission of a step from a method. See MPEP § 608.04 to § 608.04(c). See In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) and MPEP § 2163.05 for guidance in determining whether the addition of specific percentages or compounds after a broader original disclosure constitutes new matter.")

This is a new matter rejection.

***Written Description/ New Matter***

11. Claims 46, 49 and 52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 45, 48 and 51 are interpreted as being drawn to "wherein the amino acid sequence of the peptide linker is [GlyGlyGlyGlySer]n, wherein n is 3 or 4."

The examiner's search of the specification for the limitation does not identify literal support for this limitation. (MPEP 706.03(m) states in part "New matter includes not only the addition of wholly unsupported subject matter, but may also include adding specific percentages or compounds after a broader original disclosure, or even the omission of a step from a method. See MPEP § 608.04 to § 608.04(c). See In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) and MPEP § 2163.05 for

guidance in determining whether the addition of specific percentages or compounds after a broader original disclosure constitutes new matter.")

This is a new matter rejection.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 21, 33 and 45-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Little et al. (CA 2331641 or DE19819846; published 11/11/99; both cited in the IDS of 5/25/06) in view of McGuinness et al. (Nat. Biotech. 14:1149-1154 (1996); cited in the PTO 892 form of 8/8/07) and Volkel (Protein Engineering 14(10):815-823 (2001); cited in the IDS of 5/25/06).

The interpretation of Claims 21 and 23 is of record. Claims 45-50 are drawn to one or more copies of the sequence of GlyGlyGlyGlySer.

The claims were prima facie obvious at the time of the invention in view of Little, McGuinness and Volkel.

See Figure 2 of Little (DE19819846), where Little shows restriction digestion of a first linker in a first scfv; restriction digestion of a second linker in a second scfv and recombining the VH1-VL2 and the VH2-VL1 constructs into a single fused scfv diabody construct for producing libraries. Little teaches examples of nucleotide sequences encoding peptide linkers which link the hybrid scFv fragments, for example, in Fig. 3 a nucleotide sequence encoding a (Gly4Ser)4 polypeptide (p. 6 of the specification); in Figure 4 a nucleotide sequence encoding a GlyGlyProGlySer oligopeptide (p. 7 of the specification).

McGuinness discloses methods for constructing an antibody phage display library where the V regions from antibodies against the hapten phOX or Dig are constructed into two pools of scFvs repertoires having a 15-amino acid linker between each VH and VL domain, where the orientation of the domains is VH-linker-VL (p. 1150, Col. 1, ¶1). The scFv pools were recombined into a diabody format: VHA-VLB-rbs (linker)-VHB-VLA, where the linker between each VH and VL domain was "shortened" to a zero linker (p. 1150, Col. 2, ¶1) using one of two methods: ligation mediated assembly or cassette cloning where the final diabody is inserted into an expression vector. For ligation-mediated assembly, a two- (Fig 21, A-C) or three-step (Fig. 2iD) process is taught in the Materials and Methods on p. 1153, ¶2. In the three-step approach, an 800 bp fragment comprising Dig VH-phOxVL and phOxVH fragment are cut with a restriction enzyme and ligated, then the ligated fragment was mixed with a

Dig VL fragment and digested with another restriction enzyme, and then ligated to produce the diabody insert. The two-step approach comprised taking the 800 bp fragment comprising Dig VH-phOxVL and phOxVH and a phOxVH-DigVL fragment, ligating the mixture and digesting with restriction enzymes to produced the diabody insert. For cassette cloning, VHA-VLB and VHB-VLA fragments were generated by PCR extension from the scFv pools, and the fragments digested with different restriction enzymes (Fig. 2ii) to produce a DigVH-phOxVL fragment and a phOxVH-DigVL fragment with terminal restriction sites followed by assembly into the diabody (p. 1151, Col. 1, ¶2; and M & M, p. 1153, Col. 2, ¶2). The 15 amino acid linker of McGuinness is considered as reading on the linker for the first and second single scFvs and the HV and LV. The claims are not drawn to the specific order in which the VH1 and VL1 or the VH2 and VL2 should occur. In other words, McGuinness teaches a diabody format: VHA-VLB-rbs (linker)-VHB-VLA which reads on the instant claims. Thus McGuinness teaches at least two possible methods for producing a scfv diabody format or construct, but more importantly, that the ordinary artisan could predict that scfv diabody libraries were producible at the time of the invention much less functional based on McGuinness.

Volkel discloses constructing a diabody phage display library comprising single chain diabody CEA scFv/Gal scFv constructs with a randomized middle linker from where the M linker is of variable length and comprises at least one restriction site (See Figure 2A and B). Volkel discloses generating a fragment comprising GalVL-M linker-GALVH where the M linker comprises a restriction site and subcloning the fragment into the linker region for the CEA scFv where the linker region comprises two restriction

enzyme sites, BstE II and Sac I. Volkel discloses generating clones with variable linker and M-linker lengths and comprising different amino acid sequences (Tables III and IV) which are cloned into an expression vector.

One skilled in the art would have been motivated and been assured of reasonable success in having produced the instant methods at the time of the invention based on the combined disclosures of Little McGuinness and Volkel because each disclose the technology for constructing single-chain diabody phage display libraries where a scFv recognizing a first antigen comprising a linker with a restriction enzyme site and a second scFv recognizing a second antigen comprising a linker are treated with a restriction enzyme in order to obtain fragments which are then ligated in order to construct a final fragment having the VH and VL domains against the second antigen inserted between the VH and VL domains against the first antigen are assembled into the diabody phage display library. Each of the references discloses techniques involving differential restriction enzyme digestion of various fragments and the technology for selective insertion of the VH2/VL2 or VL2/VH2 pair between the VH1/VL1 or VL1/VH1 domains to generate a phage display diabody library. Each of the references teaches obtaining fragments comprising variable domains and shortening the linker between the domains in a ligation (PCR extension step). Further because the instant claimed method actually involves even fewer steps than taught by any of the reference disclosures in order to generate a scfv diabody construct, the ordinary artisan would have been motivated to obtain a process that was ensured to generate functional scfv diabody, by inserting a sequence encoding a second pair of heavy and light chain variable domains

into the open restriction site for the linker of a first pair of heavy and light chain variable domains.

Based on the combined reference disclosures, one skilled in the art could have been assured of success in introducing linkers between VH and VL domains comprising restriction sites for subcloning into or between VH and VL domains against a different antigen because the references taught that subfragments could readily be generated and where a VH/VL pair against one antigen was inserted between the VH and VL against a different antigen. Little and McGuinness teach that construction and selection from such a library is possible and it avoids unfavorable combinations (p. 1153, Col. 1, ¶2), and Volkel discloses generating single-chain diabodies with optimized linker sequences and expressed by phage display where correctly folded molecules can be screened against a variety of different target cells and antigens (p. 822, Col. 2, ¶3). Further, one skilled in the art could have readily constructed a self-ligating antibody library based on the method steps of Little, McGuinness and Volkel to produce a second library having a shorter linker in relying on restriction enzyme sites in linker to restrict out a certain length of the linker to obtain a shorter linker.

***Conclusion***

13. No claims are allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner, Art Unit 1643